REMARKS

STATUS OF THE CLAIMS:

Claims 30 and 31 have been amended. Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 are pending.

Claims 30 and 31 were amended to append the "polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2, or encoded by ATCC deposit PTA-2966" limitation. Support for this amendment may be found in the specification as originally filed. Specifically, support for this amendment may be found in original Claim 23. Applicants assert that this amendment was not made to overcome any issues related to the patentability of these claims and that Applicants right to equivalents of Claims 30 and 31 is reserved.

Claims 30 and 31 were further amended to append the "of expression relative to the expression of a reference polynucleotide" limitation. Support for this amendment may be found in the specification as originally filed. Specifically, support for this amendment may be found in Examples 3, 4, and 8. Applicants assert that this amendment was not made to overcome any issues related to the patentability of these claims and that Applicants right to equivalents of Claims 30 and 31 is reserved.

No new matter has been added. Applicants believe that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

I. Miscellaneous

The Examiner makes several statements throughout the Office Action that suggest Applicants pending claims recite a "...beta lactamase gene under the control of NFTA response elements". In the interest of correcting the record, Applicants wish to point out to the Examiner that the pending claims recite a "...beta lactamase gene under the control of NFAT response elements".

Applicants would like to remind the Examiner that the pending claims are specific to the "NFAT" species and that upon allowance of claims to this species, Applicants are entitled to have claims specific to the "CRE" species considered for Examination.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges:

> The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require[s] further research.

Applicants respectfully disagree. The claimed subject matter is specific in that it is directed to methods of identifying compounds that modulate a specific G-protein coupled receptor, HGPRBMY8, and not simply any G-protein coupled receptor. The claims further specify that the compounds identified by such method be useful for the treatment of caudate nucleus disorders, and not simply any disorder. Applicants assert that the utility is particular to the claimed subject matter and is specific.

Applicants also assert that the utility is substantial. According to the Revised Utility Examination Guidelines, an assay method for identifying compounds that themselves have a substantial utility define a "real world" context of use. Applicants assert that the compounds identified by the claimed method meet the substantial utility test as they are useful for treating specific disorders, preferably caudate nucleus disorders. Again, according to the Revised Utility Examination Guidelines, methods of treating a disorder should not be subject to U.S.C. 101 rejections since "most diseases or conditions can be treated".

The specification teaches that the HGPRBMY8 polypeptide is predominately expressed in caudate nucleus tissue of the brain. In fact, HGPRBMY8 was expressed at levels 825 fold higher relative to other tissues within the brain (paragraph 0274). Such a differential is significant and substantial. Moreover, disorders of the caudate nucleus represent significant and substantial neurological disorders, encompassing Alzheimer's, Parkinson's, Huntington's, depression, and schizophrenia, among others. Although there are some promising treatments for a few of these disorders either currently available or under development (McMurray, C., TINS, 11:S32-S38 (2001); Sonowalla, S. B., et al., CNS Drugs, 15(10)765-776 (2001); Thaker, G.K., et al., Nat. Med., 7(6)667-671 (2001); submitted concurrently herewith), the fact remains that there are no cures and therapeutic intervention remains the only viable alternative for treatment aside from surgery. The association of the caudate nucleus to neurological disorders is well known (Yoshida, M., Meuro Res., 12:31-40 (1991)). Applicants believe the claimed utility is substantial and does not represent a throw-away utility.

According to a 1996 study, G-protein coupled receptors represent 45% of all drug targets for present-day therapies and continue to represent a significant focal point for drug discovery (J. Drews, Science, 287:1960-1964 (2000), submitted concurrently). Since the claimed invention relates to methods of screening for compounds that modulate a particular G-protein coupled receptor, HGPRBMY8, and whereby these compounds have a specified utility, namely, for the treatment of caudate nucleus disorders, Applicants assert that one skilled in the art would recognize this utility as being specific, substantial, and representing a "real-world" context of use.

In addition to a specific and substantial utility, as Applicants have asserted, the Revised Utility Examination Guidelines require that such utility be credible (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Clearly, specific and substantial caudate nucleus disorder utilities asserted by Applicants are credible, particularly in light of the significant differential expression in caudate nucleus tissue. Such assertions are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." See, Revised Utility Guidelines Training Materials.

Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of

such a statement. Significantly, no such countervailing evidence has been provided. If such evidence is available to the examiner, Applicants request that the Examiner provide an affidavit pursuant to 37 C.F.R. § 1.104(d)(2) containing evidence substantiating this position. Because Applicants have asserted specific and substantial utilities that are credible, Applicants have also complied with the credible utility requirement.

According to the Examiner, a specific and substantial utility is one that identifies a "real world" context of use for the claimed invention which does not require further research. By stating that the claimed invention is not supported by a specific and substantial utility, the Examiner is alleging that the claimed invention does not identify a "real world context of use and that additional research is required". Applicants assert that the claimed caudate nucleus utilities do represent a "real world" context of use since the methods of screening G-protein coupled receptors to identify modulators of the same are common pharmaceutical practice, and the fact that caudate nucleus disorders are "real" disorders afflicting the "world" today.

Applicants do not agree that additional research would be required to determine the functions of the claimed molecules since Applicants disclosure already teaches that the subject HGPRBMY8 polypeptide is a functional G-protein coupled receptor (paragraphs 0046-0051, and Figures 11-16A-D, and Example 7). Moreover, Applicants also disagree that further research would be required to identify a disease that can be treated or diagnosed with the claimed molecules since Applicants disclosure already identifies caudate nucleus disorders, particularly neurological disorder; Parkinson's disease; neuropathic pain; psychotic disorders; severe mental retardation; dyskinesias, Huntington's disease; Gilles dela Tourett's syndrome; Sydenham chorea; major depressive disorder; obsessive-compulsive disorder; movement type disorders; anxiety; schizophrenia; manic depression; delirium; dementia; and neoplastic diseases of the brain, as diseases that can be specifically treated or diagnosed with modulators of the subject HGPRBMY8 polypeptide.

b. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 101, for failure to identify the ligand of the HGPRBMY8 polypeptide and the specific biological function of the polypeptide. The Examiner further asserts that "without a defined ligand or biological function, one skilled in the art would not be able to recognize the specific and substantial use of the polypeptide of SEQ ID NO:2 and consequently the claimed method of screening for candidate compounds which modulate the activity of the polypeptide of SEQ ID NO:2".

Applicants do not agree and assert that one skilled in the art would acknowledge that identification of a ligand specific to HGPRBMY8 is not required to practice Applicant's claimed method of screening for compounds that modulate the function of HGPRBMY8 polypeptide.

Specifically, Applicant's claimed invention takes advantage of the constitutive activation of G-protein coupled receptors that occurs in response to over expression of the same. As Applicants specification points out in paragraphs 0252 and 0253, such activation is known in the art as evidenced by the constitutive activation observed for the beta 2 adrenergic receptor in transgenic mice upon overexpression (Kypson et al., Gene Therapy., 6:1298-304 (1999); Dorn et al., PNAS, 96:6400-5 (1999); submitted concurrently herewith). Morever, Applicants specification confirms such activation as evidenced by the ability of HGPRBMY8 to constitutively activate the NFAT and CRE signal transduction pathway elements upon overexpression of HGPRBMY8. Applicants expressly assert that identification of the HGPRBMY8 ligand is not required to identify modulators of HGPRBMY8 in accordance with Applicants invention as claimed.

Applicants further assert that one skilled in the art would acknowledge that identification of a ligand specific to HGPRBMY8 is also not required to identify the biological function of HGPRBMY8, and in particular any diseases associated with HGPRBMY8. One skilled in the art would appreciate that modern assays for assessing differential expression of a particular protein in a diseased tissue relative to a normal tissue is sufficient to associate that protein to the incidence of that disease (see, for example, Kim, S.Y., et al., J Biol Chem.,274(43):30715-21 (1999); Tanaka, S., Neuroscience, 60(1):37-48 (1994); and Friess H., et al., J Clin Oncol.,19(9):2422-32 (2001); submitted concurrently herewith). Applicants wish to point out to the Examiner that Applicants specification already associates the HGPRBMY8 polypeptide of the invention with the incidence of caudate nucleus disorders, and that identification of the ligand of HGPRBMY8 is not required.

The Examiner also states that the biological function of GPCRs vary widely despite the fact that they share "certain structural motifs and features of signal transduction pathways" and cites Ji et al., J. Biol. Chem. 273:17299-17302 (1998).

Applicants do not refute that the biological function of GPCRs varies widely as stated by Ji et al. However, Applicants have provided evidence that the subject HGPRBMY8 polypeptide is capable of constitutive coupling to G-proteins involved in a signaling pathway known to be mediated by Gq/11or G alpha 15/16 or Gs coupled receptors that inhibit NFAT response elements. Applicants assert that the subject HGPRBMY8 polypeptide is a G-protein coupled receptor based upon the

functional evidence, in conjunction with the sequence analysis and structural features disclosed in the instant specification.

c. The Examiner also alleges that "methods for the treatment or prevention of cancers, immune disorders, or neurological disorders" are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use". The Examiner further alleges:

> The disclosure neither identifies the biological functions of the claimed proteins nor any disorders that are associated with the claimed molecules. Clearly, further research would be required to determine the functions of the claimed molecules or to identify a disease that can be treated or diagnosed with the claimed molecules. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Applicants do not agree. As Applicants have asserted above, the claimed caudate nucleus utilities do represent a "real world" context of use since the methods of screening G-protein coupled receptors to identify modulators of the same are common pharmaceutical practice, and the fact that caudate nucleus disorders, are "real" disorders afflicting the "world" today.

In response to the Examiners allegation that the instant disclosure neither identifies the biological functions of the claimed protein/nucleic acid nor any disorders that are associated with the claimed molecules, and that there is no link established between the instantly claimed molecules and a specific disorder, Applicants disagree. Applicants disclosure teaches that HGPRBMY8 transcripts are differentially expressed in caudate nucleus with up to 825 fold difference in expression relative to other cancer cell lines tested. Due to the significant differential expression, Applicants assert that one skilled in the art would recognize the importance of this result and *reasonably believe* that HGPRBMY8 is associated with caudate nucleus disorders.

As will be recognized, the patent laws do not require that a specification actually demonstrate use of a claimed invention. Rather, it is established law that a disclosure is enabling so long as it contains information which would lead one of ordinary skill in the art to *reasonably believe* the claimed invention has utility. *In re Barr*, 170 U.S.P.Q. 330 (C.C.P.A. 1971). In the absence of evidence or apparent reason why claimed compounds do not possess the disclosed utility, the allegation of utility in the specification *must* be accepted as correct. *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978). Applicants assert that one skilled in the art would reasonably believe

that the compounds identified by the claimed invention would be useful for treating caudate nucleus disorders based upon the disclosed expression profile.

In response to the Examiners allegation that further research would be required to determine the functions of the claimed molecules or to identify a disease that can be treated or diagnosed with the claimed molecules, Applicants disagree. Applicants do not agree that additional research would be required to determine the functions of the claimed molecules since Applicants disclosure already teaches that the subject HGPRBMY8 polypeptide is a functional G-protein coupled receptor. Moreover, Applicants also disagree that further research would be required to identify a disease that can be treated or diagnosed with the claimed molecules since Applicants disclosure already identifies caudate nucleus disorders as a disease that can be treated with modulators of the subject HGPRBMY8 polypeptide.

The Examiner also alleges that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion", and cites Brenner v. Manson. Applicants do not agree with the Examiners allegation nor do Applicants agree with the Examiners application of Brenner v. Manson to the pending claims of the instant application. At issue in Brenner was whether a chemical process for synthesizing chemical compounds was patentable for an application that did not disclose any utility for the disclosed compounds. Applicants assert that the captioned patent application already discloses the utility of the compounds identified by the claimed method and do not agree that Brenner v. Manson applies to the instant application.

Applicants wish to point out to the Examiner that the pending claims are not directed to methods of treating or preventing "immune disorders" as alleged by the Examiner. Applicants also wish to point out that the pending claims are not directed to methods of diagnosing "brain-related disorders or for monitoring response to therapy in humans" as alleged by the Examiner. Applicants assert that the claimed invention is directed to methods of screening for candidate compounds capable of modulating the activity of the HGPRBMY8 receptor polypeptide.

d. The Examiner also alleges that the invention lacks a well-established utility. Applicants disagree. According to the Revised Utility Examination Guidelines, a well-established utility is a specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of the material. Applicants specification teaches that modulators of HGPRBMY8 identified by the claimed method are useful for treating caudate nucleus disorders. Such a utility is specific since it is directed to a single polypeptide,

HGPRBMY8, and not to all G-protein coupled receptors. Such a utility is substantial since methods of screening G-protein coupled receptors to identify modulators are common pharmaceutical practice. According to the Revised Utility Examination Guidelines, an assay method for identifying compounds that themselves have a substantial utility define a "real world" context of use. Applicants assert that the compounds identified by the claimed method meet the substantial utility test as they are useful for treating specific disorders, caudate nucleus disorders. Again, according to the Revised Utility Examination Guidelines, methods of treating a disorder should not be subject to U.S.C. 101 rejections since "most diseases or conditions can be treated".

Applicants further assert that the claimed invention is credible. Applicants assert that one skilled in the art would believe that the compounds identified by the claimed method would be useful for treating caudate nucleus disorders, based upon the novel association of HGPRBMY8 to such disorders. In addition, Applicants also submit that the Examiner has not provided any evidence or reasons indicating that the claimed compounds would not possess the disclosed utilities. In the absence of such a showing, the utilities recited in the specification fully satisfy the requirements of §101. *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978)(in the absence of evidence or apparent reason why claimed compounds do not possess the disclosed utility, the allegation of utility in the specification must be accepted as correct).

The Examiner also alleges that simply being a putative G-protein coupled receptor does not endow the claimed molecules with a well-established utility. Applicants assert that the claimed invention has a well-established utility for the reasons specified *supra,* in conjunction with Applicants novel association of HGPRBMY8 to caudate nucleus disorders, and believe the Examiners allegation is moot.

The Examiner also alleges that the HGPRBMY8 polypeptide "does not have immediately practical application", and that "a method of using the polypeptide for screening a modulator of the polypeptide consequently does not have a patentable utility". Applicants disagree and again assert that the claimed invention has a well-established utility for the reasons specified *supra,* in conjunction with Applicants novel association of HGPRBMY8 to caudate nucleus disorders, and also believe the Examiners allegation is moot.

The Examiner also states that no art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the compounds. Applicants acknowledge the Examiners statement as implying the overall novelty of Applicants claimed method. Applicants agree that Applicants disclosure is the first to assign a

property (i.e., association of HGPRBMY8 to caudate nucleus disorders) and an activity (i.e., demonstration of functional coupling of HGPRBMY8 to a G-protein). Applicants also assert that another non-asserted utility is not required for the claimed method or the compounds identified by said method since Applicants believe that said method and compounds have a well-established utility as discussed herein.

III. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility and that "one skilled in the art clearly would not know how to use the claimed invention".

Applicants disagree and do not believe that a rejection under 35 U.S.C. § 112, first paragraph, is proper is consideration of Applicants assertions herein that the claimed invention represents a specific and substantial asserted utility and a well-established utility

b. The Examiner further alleges that "even if the claimed method of screening candidate compounds were to have a patentable utility, the instant disclosure would not be found to be enabling for the full-scope of the claimed invention." The Examiner also provides a list of several factors that are considered when determining whether a disclosure satisfies the enablement requirement, which includes "(i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims"..

Applicants disagree and assert that the invention embraced by Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 is enabling according to the teachings of the specification, as originally filed. Relative to Examiners requirement (i), Applicants assert that the quantity of experimentation required is minimal since screening G-protein coupled receptors to identify modulators are common pharmaceutical practice as discussed herein. Applicants assert that the pending claims are enabled and that requirement (i) is met by the specification as originally filed.

Relative to Examiners requirement (ii), Applicants assert that the specification as originally filed provides significant direction and guidance in sufficient detail to enable one skilled in the art to practice the claimed invention. Specifically, Applicants specification teaches that the HGPRBMY8

polypeptide is not only a GPCR, but a functional GPCR based upon Applicants demonstration of functional coupling. Applicants also wish to point out to the Examiner that the same methods used to demonstrate HGPRBMY8 functional coupling are encompassed by the pending claims. Since Applicants have reduced the claimed invention to practice and teach the methods used to accomplish the same, Applicants assert that the pending claims are enabled and that requirement (ii) is met by the specification as originally filed.

Relative to Examiners requirement (iii), Applicants assert that working examples have been provided in the specification as filed. Specifically, Examples 1, 2, 3, 4, 7, 8, and 9 are "working examples". Example 3, 4, 7, and 8, in particular, are relevant to the pending claims. Moreover, Example 7 teaches the method used to demonstrate functional HGPRBMY8 coupling and is encompassed by the pending claims. Applicants assert that the pending claims are enabled and that requirement (iii) is met by the specification as originally filed.

Relative to Examiners requirement (iv), Applicants assert that the nature of screening GPCRs to identify modulators thereof represents standard pharmaceutical practice, and thus is within the level of skill of the artisan. Applicants assert that the pending claims are enabled and that requirement (iv) is met by the specification as originally filed.

Relative to Examiners requirement (v), Applicants assert that the method embraced by the pending claims is novel and represents the first description of such a screening method for the HGPRBMY8 polypeptide. Applicants also assert that Applicants specification represents the first association of HGPRBMY8 to caudate nucleus disorders. Applicants assert that the pending claims are enabled and that requirement (v) is met by the specification as originally filed.

Relative to Examiners requirement (vi), Applicants assert that the method embraced by the pending claims is within the level of skill of those in the art. As discussed herein, the method embraced by the pending claims has been reduced to practice and taught in Applicants specification as originally filed. In addition, since methods of screening for GPCR modulators represents standard pharmaceutical practice, the skilled artisan would certainly be able to practice the invention based upon the teachings of Applicants specification. Applicants assert that the pending claims are enabled and that requirement (vi) is met by the specification as originally filed.

Relative to Examiners requirement (vii), Applicants assert that the method embraced by the pending claims is predictable to the extent that it is possible to identify modulators of the HGPRBMY8 polypeptide using the claimed method. Moreover, the fact that Applicants have demonstrated functional coupling of HGPRBMY8 further confirms the predictability of the claimed

method since there is no doubt that HGPRBMY8 is a functional GPCR. Applicants assert that the pending claims are enabled and that requirement (vii) is met by the specification as originally filed.

Relative to Examiners requirement (viii), Applicants assert that the breadth of the pending claims is reasonable as they are specific to the HGPRBMY8 polypeptide, and do not read on methods of screening other GPCR polypeptides. Moreover, the fact that the Examiner has not cited any art of record represents a further confirmation that the breadth of Applicants pending claims are reasonable. Applicants assert that the pending claims are enabled and that requirement (viii) is met by the specification as originally filed.

Applicants wish to point out to the Examiner that even if the Examiner was not persuaded by one or more of Applicants assertions above, that "it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole..." (Training Materials with respect to 35 U.S.C. section 12, first paragraph). Applicants assert that the pending claims are thus enabled.

c. The Examiner further alleges that the "instant disclosure fails to enable such a claimed method of screening for a candidate compound which is useful for treatment of disorders of the caudate nucleus, it would require undue experimentation for one skilled in the art to make and use the claimed method embraced by the instant claim". Specifically, the Examiner alleges that the instant disclosure fails to identify the biological functions of the claimed polypeptide. Applicants disagree and assert that Applicants specification sufficiently demonstrates that HGPRBMY8 is a functional GPCR. Moreover, Applicants also assert that Applicants specification is the first association of HGPRBMY8 to caudate nucleus disorders. Applicants assert that the Examiners biological function requirement is met by Applicants specification.

The Examiner also alleges that the instant disclosure "fails to demonstrate the existence of [a] link established between the molecules of the present invention and disorders of the caudate nucleus, and fails to demonstrate the likelihood of the success of treating disorders of the caudate nucleus with a potential candidate compound". As discussed herein, Applicants assert that the instant specification adequately demonstrates an association between the HGPRBMY8 polypeptide to caudate nucleus disorders based upon the observed 825 fold differential expression of HGPRBMY8 in caudate nucleus tissue relative to other tissues in the brain. Clearly, HGPRBMY8 is essential to normal caudate nucleus function based upon such strong differential expression. Further, Applicants

assert that one skilled in the art would appreciate the role of HGPRBMY8 in caudate nucleus function and would credibly believe that aberrant HGPRBMY8 function could be associated with the incidence of caudate nucleus disorders. Based upon this novel association, in conjunction with the surprising differential expression pattern, Applicants assert that one skilled in the art would "reasonably" believe that the molecules identified by the present invention would be useful for treating caudate nucleus disorders.

Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Significantly, no such countervailing evidence has been provided. Because Applicants have asserted specific and substantial utilities that are credible, Applicants have also complied with the credible utility requirement.

The Examiner further alleges that the "instant disclosure fails to provide sufficient guidance, information, or working examples on how to treat these neurological disorders". Applicants disagree and assert that Applicants specification adequately teaches pharmaceutical compositions and their administration in sufficient detail to enable one skilled in the art to practice the invention (see paragraphs 0234 to –253, for example).

The Examiner further alleges that the "prior art does not provide compensatory teachings to enable one skilled in the art to treat the broadly claimed disorders using a candidate screened by the claimed method". Applicants disagree as caudate nucleus disorders are disorders that are treatable, and thus one skilled in the art could rely on the compensatory teachings in the art to practice the claimed invention. (McMurray, C., TINS, 11:S32-S38 (2001); Sonowalla, S. B., et al., CNS Drugs, 15(10)765-776 (2001); Thaker, G.K., et al., Nat. Med., 7(6)667-671 (2001); submitted concurrently herewith).

d. The Examiner further alleges "the instant disclosure fails to enable such a claimed method of screening for a candidate compound which is useful for treatment of disorders of the caudate nucleus, it would require undue experimentation for one skilled in the art to make and use the claimed method embraced by the instant claim".

Applicants disagree as undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 443 F.2d 1386, 1390-1391, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that are considered in

determining whether an amount of experimentation is undue have been listed in In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. Id.

As Applicants have asserted herein, Applicants specification provides adequate guidance to practice the invention, includes working examples that demonstrate the functional coupling activity of the HGPRBMY8 polypeptide, working examples that demonstrate the caudate nucleus expression profile, and working examples that demonstrate the claimed method. Applicants have also provided examples of caudate nucleus disorders that illustrate that such disorders are therapeutically tractable. Applicants have also asserted that methods of screening G-protein coupled receptors to identify modulators of the same are common pharmaceutical practice. Applicants assert that the pending claims are fully enabled and would not require undue experimentation for a skilled artisan to make and use the invention.

IV. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 112, second paragraph, alleging that the claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". More particularly, the Examiner alleges that "Claim 23 is indefinite because the steps of the method do not necessarily achieve the goal set forth in the claim preamble. It is unclear what is detected or measured that renders one able to select a candidate compound".

Applicants disagree. The preamble of Claim 23 specifically states that it is directed to a "method of screening for candidate compounds capable of modulating the activity of a G-protein coupled receptor". The steps of the method clearly state that the criterion for selecting a candidate compound would be those "test compounds that modulate the activity of the G-protein coupled receptor polypeptide".

Applicants also wish to point out to the Examiner that the preamble of Claim 23, as drafted, merely states the purpose or intended use of the invention. The purpose is to find "compounds that modulate the activity of a G-protein coupled receptor", which is the same goal that is met by the last stated step of Claim 23. Since the method is to identify modulators of HGPRBMY8, identifying

compounds that affect the activity of HGPRBMY8 is a sufficient enough criterion to select a candidate compound. Necessarily, Claim 23 encompasses the identification of agonists and antagonists of HGPRBMY8 as drafted, which Applicants believe they are so entitled. Applicants assert that Claim 23 is definite and do not agree with the Examiners allegation.

b. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 112, second paragraph, alleging that the claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". More particularly, the Examiner alleges that "Claims 30 and 31 are indefinite because each claim recites "the polypeptide". It is unclear whether it refer[s] to SEQ ID NO:2, beta lactamase gene, or G alpha 15.".

Applicants disagree and assert that the only molecule referred to as a "polypeptide" in Claims 30 and 31, and the claims from which they depend from, specifically Claims 26, 25, 24, and 23, is the "polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2, or encoded by ATCC deposit PTA-2966" as stated in Claim 23. Applicants assert that Claims 30 and 31 have proper antecedent basis. However, Applicants have amended Claims 30 and 31 to add the "polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2, or encoded by ATCC deposit PTA-2966" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot in light of the amendments. Applicants reserve the right to prosecute these claims in their original form in related applications.

c. The Examiner has rejected Claims 23-26, 28, 30, 31, 34-36, 40, 41, and 44-46 under 35 U.S.C. § 112, second paragraph, alleging that the claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". More particularly, the Examiner alleges that "Claims 30 and 31 are indefinite because each claim recites "high levels" or "low levels". It is unclear what the metes and bounds of the term are".

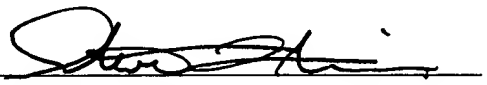
Applicants disagree. However, Applicants have amended Claims 30 and 31 to add the "of expression relative to the expression of a reference polynucleotide" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot in light of the amendments. Applicants reserve the right to prosecute these claims in their original form in related applications.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A one-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $100 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



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